COMBINATION THERAPIES FOR B-CELL LYMPHOMAS COMPRISING ADMINISTRATION OF ANTI-CD20 ANTIBODY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a divisional application of U.S. patent application Ser. No. 11/840,956, filed Aug. 18, 2007, which is a continuation of U.S. patent application Ser. No. 10/196,732, filed Jul. 17, 2002 (abandoned), which is a continuation of U.S. patent application Ser. No. 09/372,202, filed Aug. 11, 1999, (now U.S. Pat. No. 6,455,043) which claims priority under 35 U.S.C. Section 119(e) and the benefit of U.S. Provisional Application Ser. No. 60/096,180 filed Aug. 11, 1998, the disclosures of which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

[0002] The invention relates to the use of anti-CD20 antibodies or fragments thereof in the treatment of B-cell lymphomas, particularly the use of such antibodies and fragments in combined therapeutic regimens.

BACKGROUND OF THE INVENTION

[0003] The use of antibodies to the CD20 antigen as diagnostic and/or therapeutic agents for B-cell lymphoma has previously been reported. CD20 is a useful marker or target for B-cell lymphomas as this antigen is expressed at very high densities on the surface of malignant B-cells, i.e., B-cells wherein unabated proliferation can lead to B-cell lymphomas.

[0004] CD20 or Bp35 is a B-lymphocyte-restricted differentiation antigen that is expressed during early pre-B-cell development and remains until plasma cell differentiation. It is believed by some that the CD20 molecule may regulate a step in the B-cell activation process which is required for cell cycle initiation and differentiation. Moreover, as noted, CD20 is usually expressed at very high levels on neoplastic ("tumor") B-cells. The CD20 antigen is appealing for targeted therapy, because it does not shed, modulate, or internalize.

[0005] Previous reported therapies involving anti-CD20 antibodies have involved the administration of a therapeutic anti-CD20 antibody either alone or in conjunction with a second radiolabeled anti-CD20 antibody, or a chemotherapeutic agent.

[0006] In fact, the Food and Drug Administration has approved the therapeutic use of one such anti-CD20 antibody, RITUXAN®, for use in relapsed and previously treated low-grade non-Hodgkin's lymphoma (NHL). Also, the use of RITUXAN® in combination with a radiolabeled murine anti-CD20 antibody has been suggested for the treatment of B-cell lymphoma.

[0007] However, while anti-CD20 antibodies and, in particular, RITUXAN® (U.S.; in Britain, MABTHERA®; in general Rituximab), have been reported to be effective for treatment of B-cell lymphomas, such as non-Hodgkin's lymphoma, the treated patients are often subject to disease relapse. Therefore, it would be beneficial if more effective treatment regimens could be developed. More specifically, it would be advantageous if anti-CD20 antibodies had a beneficial effect in combination with other lymphoma treatments, and if new combined therapeutic regimens could be developed to lessen the likelihood or frequency of relapse. Also, it would be helpful if current treatment protocols for B-cell lymphoma were improved whereby patients with lymphomas which are refractory to other treatment methods could be treated with chimeric or radiolabeled anti-CD20 antibodies. It would also be helpful if treatment with anti-CD20 antibodies, particularly in combination with other treatments, could be used as therapy for other types of lymphoma besides low grade, follicular non-Hodgkin's lymphoma (NHL).

SUMMARY OF THE INVENTION

[0008] The present invention discloses combined therapeutic treatments for B-cell lymphomas, and reports the benefits of treating relapsed or refractory B-cell lymphomas with chimeric and radiolabeled anti-CD20 antibodies. In particular, it has been found that treatment with anti-CD20 antibody provides a beneficial synergistic effect when administered in combination with cytokines, radiotherapy, myeloablative therapy, or chemotherapy. Surprisingly, patients who had prior bone marrow or stem cell transplantation had an unexpected increase in the over-all response rate when compared with patients with no prior therapy.

DETAILED DESCRIPTION OF THE INVENTION

[0009] This invention encompasses combined therapeutic regimens for the treatment of B-cell lymphomas. In general, such methods include a method for treating relapsed B-cell lymphoma, where a patient having prior treatment for lymphoma has relapsed and is administered a therapeutically effective amount of a chimeric anti-CD20 antibody. Such prior treatments can include, for example, previous treatment with anti-CD20 antibodies, treatments which included a bone marrow or stem cell transplantation, radiotherapy and chemotherapy. The previous chemotherapy may be selected from a wide group of chemotherapeutic agents and combination regimens, including CHOP, ICE, Mitozantrone, Cytarabine, DVP, ATRA, Idarubicin, hoelzer chemotherapy regime, La La chemotherapy regime, ABVD, CEOP, 2-CdA, FLAG & IDA with or without subsequent G-CSF treatment), VAD, M & P, C-Weekly, ABCM, MOPP and DHAP.

[0010] Also included in the methods of the invention are methods for treating a subject having B-cell lymphoma wherein the subject is refractory for other therapeutic treatments, including all those listed above, i.e., treatment with chimeric anti-CD20 antibody, treatments which included a bone marrow or stem cell transplantation, radiotherapy and chemotherapy. In particular, encompassed are methods of treating a patient who has not exhibited appreciable tumor remission or regression after administration of a chimeric anti-CD20 antibody, comprising administering to said patient a radiolabeled anti-CD20 antibody.

[0011] In particular, the methods of treating a patient with a radiolabeled antibody after a chimeric antibody are performed whereby the radiolabeled anti-CD20 antibody is administered from about one week to about two years after said administration of said chimeric anti-CD20 antibody. More particularly, the radiolabeled anti-CD20 antibody is administered from about one week to about nine months after said administration of said chimeric anti-CD20 antibody.

[0012] While any anti-CD20 antibodies can be used for the methods of the present invention, a preferred chimeric antibody is C2B8 (IDEC Pharmaceuticals, Rituximab). A preferred radiolabeled antibody is Y2B8, which is a murine